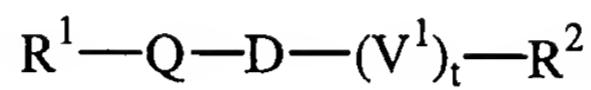


CLAIMS

What is claimed is:

5

1. A compound of Formula I



I

or a pharmaceutically acceptable salt thereof,

wherein:

10  $R^1$  and  $R^2$  independently are selected from:

$C_1-C_6$  alkyl;

Substituted  $C_1-C_6$  alkyl;

$C_2-C_6$  alkenyl;

Substituted  $C_2-C_6$  alkenyl;

15  $C_2-C_6$  alkynyl;

Substituted  $C_2-C_6$  alkynyl;

$C_3-C_6$  cycloalkyl;

Substituted  $C_3-C_6$  cycloalkyl;

$C_3-C_6$  cycloalkyl-( $C_1-C_6$  alkyl);

20 Substituted  $C_3-C_6$  cycloalkyl-( $C_1-C_6$  alkyl);

3- to 6-membered heterocycloalkyl;

Substituted 3- to 6-membered heterocycloalkyl;

3- to 6-membered heterocycloalkyl-( $C_1-C_6$  alkyl);

Substituted 3- to 6-membered heterocycloalkyl-( $C_1-C_6$  alkyl);

25 Phenyl-( $C_1-C_6$  alkyl);

Substituted phenyl-( $C_1-C_6$  alkyl);

Naphthyl-( $C_1-C_6$  alkyl);

Substituted naphthyl-( $C_1-C_6$  alkyl);

5-, 6-, 9-, and 10-membered heteroaryl-( $C_1-C_6$  alkyl);

30 Substituted 5-, 6-, 9-, and 10-membered heteroaryl-( $C_1-C_6$  alkyl);

Phenyl;

Substituted phenyl;

Naphthyl;

Substituted naphthyl;  
5-, 6-, 9-, and 10-membered heteroaryl;  
Substituted 5-, 6-, 9-, and 10-membered heteroaryl;  
 $R^3O-(C_1-C_6$  alkylenyl);  
5 Substituted  $R^3O-(C_1-C_6$  alkylenyl);  
Phenyl- $O-(C_1-C_8$  alkylenyl);  
Substituted phenyl- $O-(C_1-C_8$  alkylenyl);  
Phenyl- $S-(C_1-C_8$  alkylenyl);  
Substituted phenyl- $S-(C_1-C_8$  alkylenyl);  
10 Phenyl- $S(O)-(C_1-C_8$  alkylenyl);  
Substituted phenyl- $S(O)-(C_1-C_8$  alkylenyl);  
Phenyl- $S(O)_2-(C_1-C_8$  alkylenyl); and  
Substituted phenyl- $S(O)_2-(C_1-C_8$  alkylenyl);  
wherein  $R^1$  and  $R^2$  are not both selected from:  
15  $C_1-C_6$  alkyl;  
 $C_2-C_6$  alkenyl;  
 $C_2-C_6$  alkynyl; and  
 $C_3-C_6$  cycloalkyl;  
Each  $R^3$  independently is selected from:  
20 H;  
 $C_1-C_6$  alkyl;  
Substituted  $C_1-C_6$  alkyl;  
 $C_3-C_6$  cycloalkyl;  
Substituted  $C_3-C_6$  cycloalkyl;  
25 Phenyl- $(C_1-C_6$  alkylenyl);  
Substituted phenyl- $(C_1-C_6$  alkylenyl);  
Naphthyl- $(C_1-C_6$  alkylenyl);  
Substituted naphthyl- $(C_1-C_6$  alkylenyl);  
5-, 6-, 9-, and 10-membered heteroaryl- $(C_1-C_6$  alkylenyl);  
30 Substituted 5-, 6-, 9-, and 10-membered heteroaryl- $(C_1-C_6$  alkylenyl);  
Phenyl;  
Substituted phenyl;

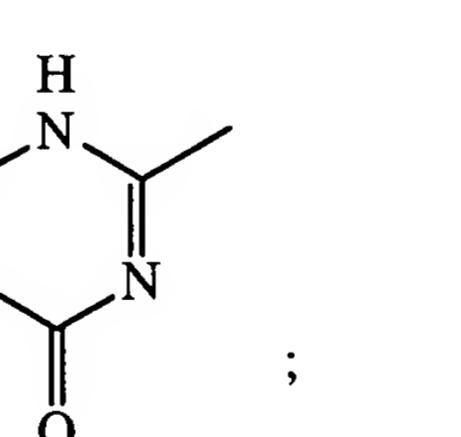
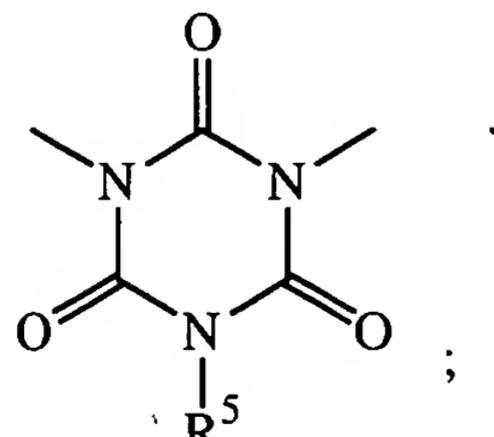
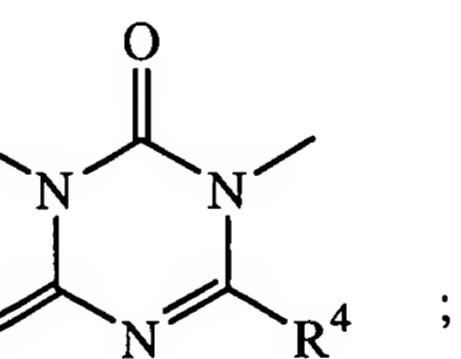
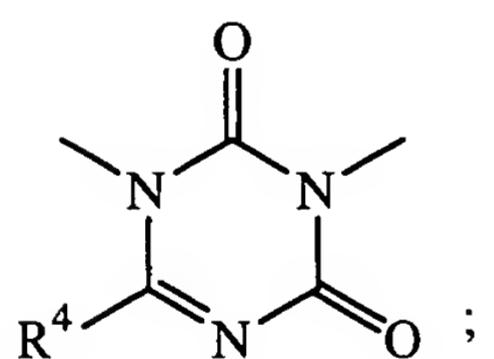
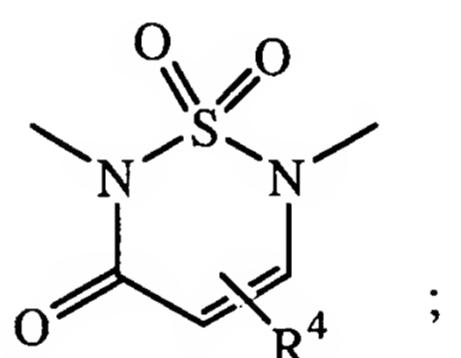
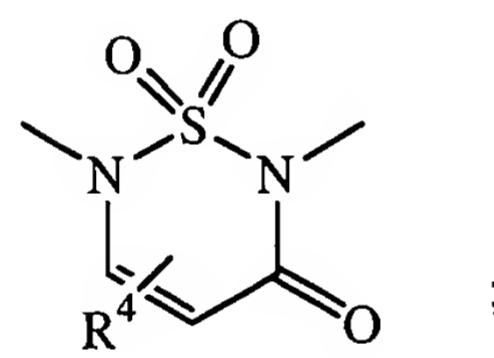
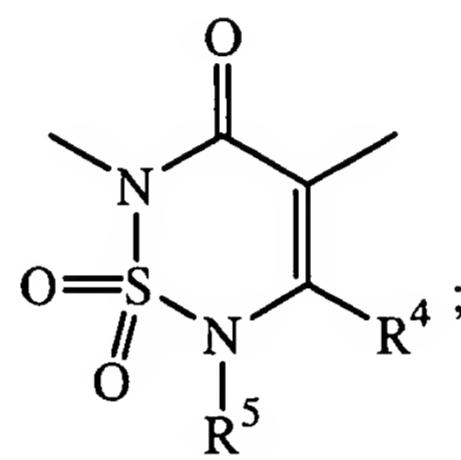
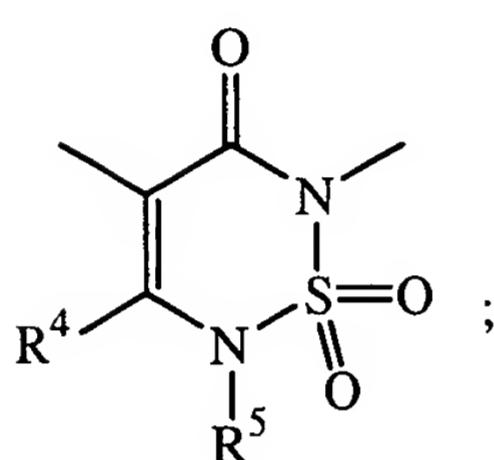
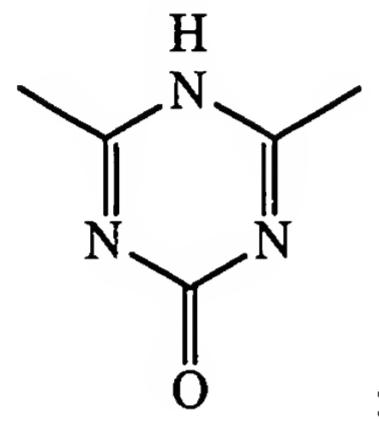
Naphthyl;

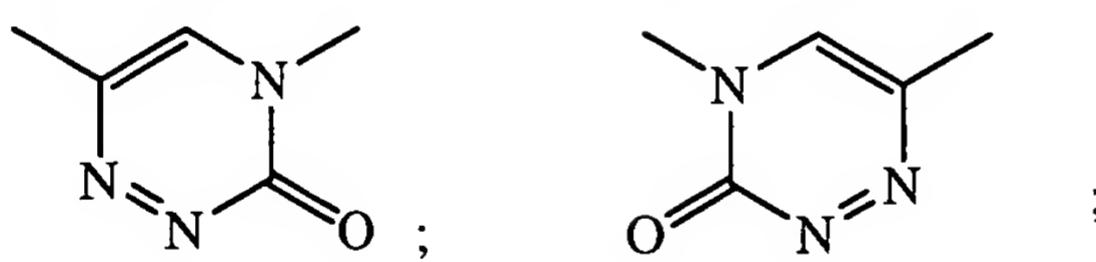
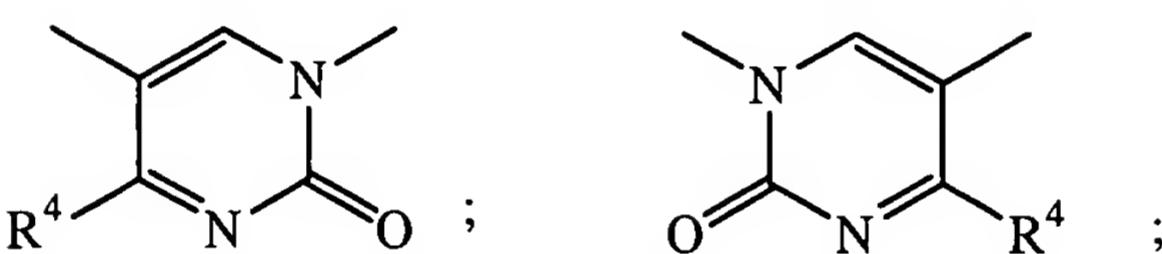
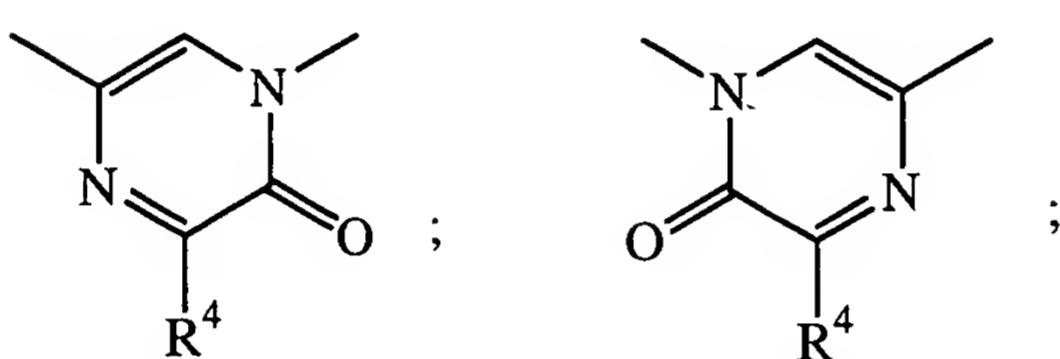
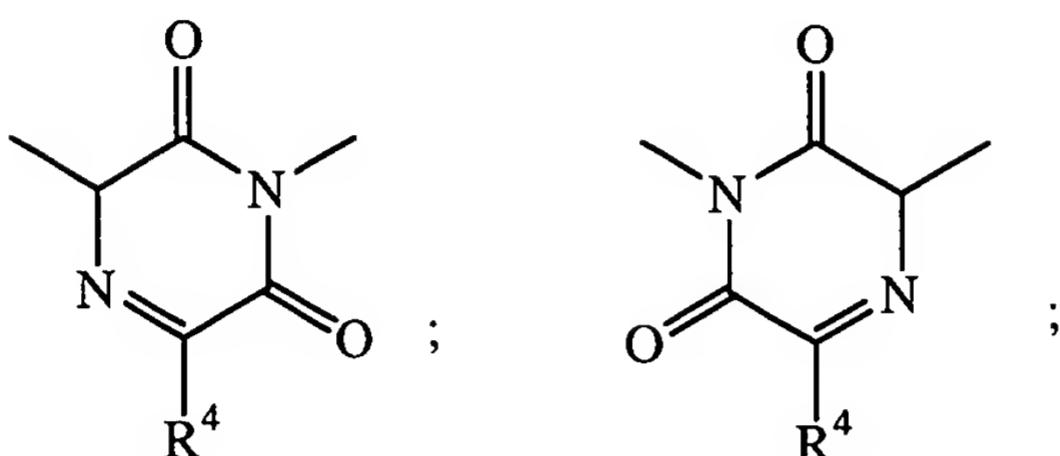
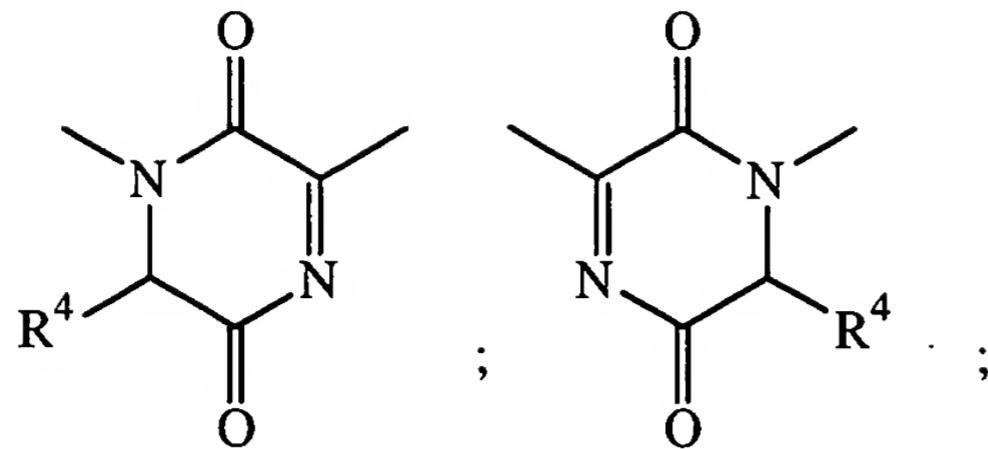
Substituted naphthyl;

5-, 6-, 9-, and 10-membered heteroaryl;

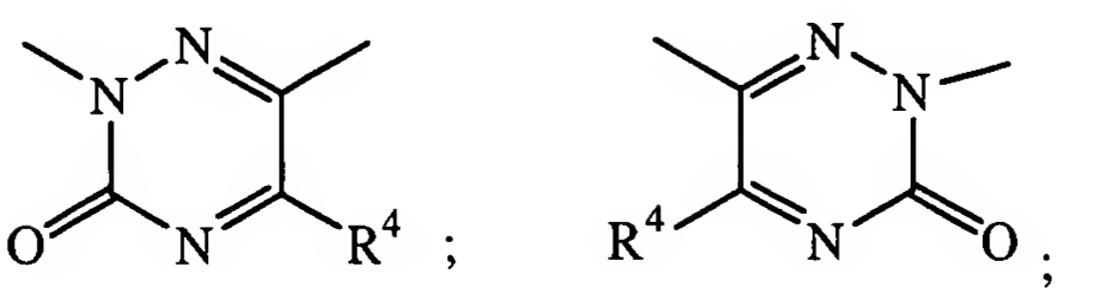
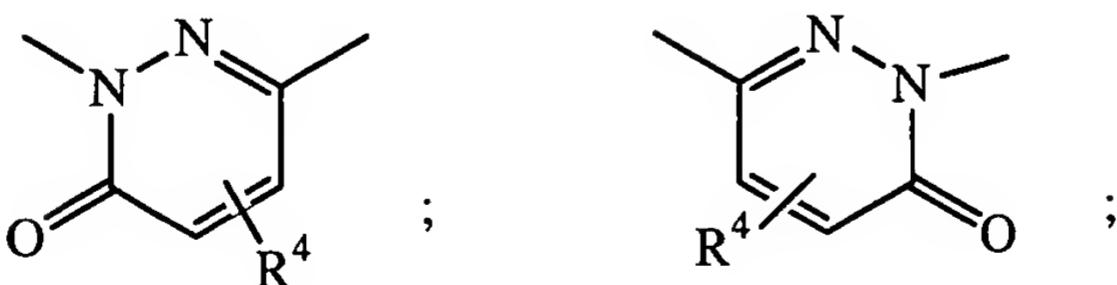
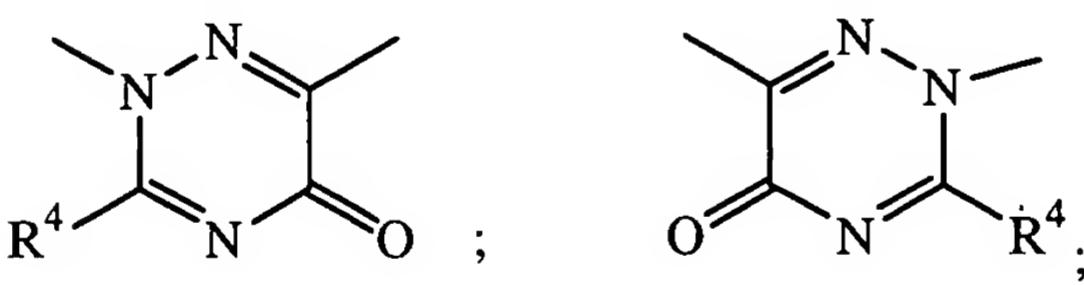
Substituted 5-, 6-, 9-, and 10-membered heteroaryl;

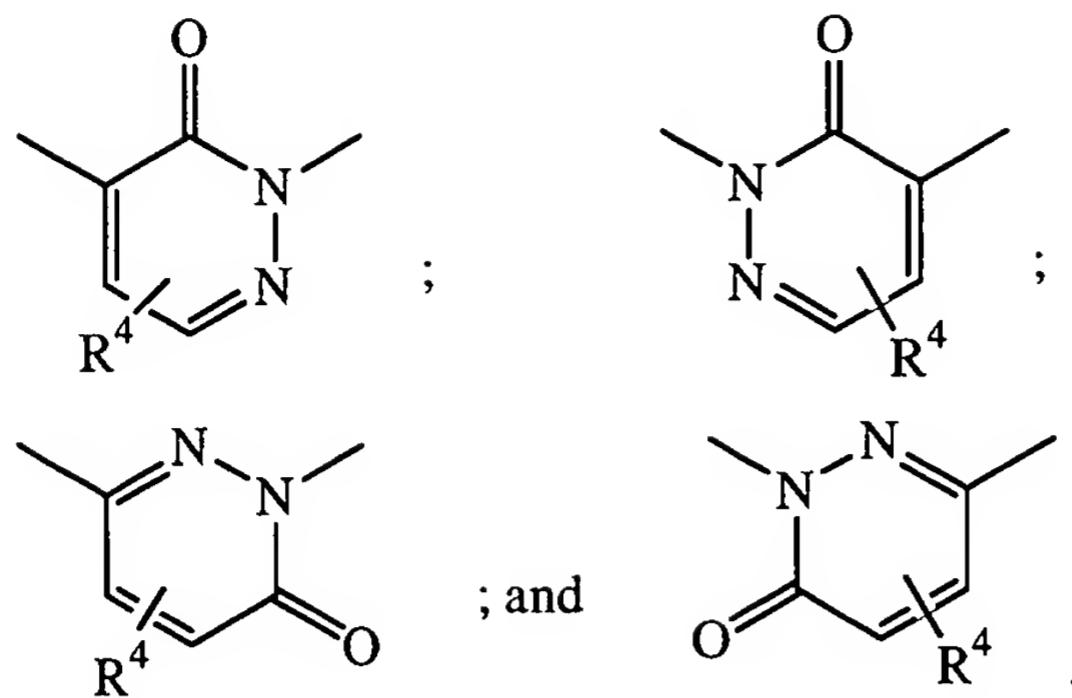
5 D is a heteromonocyclic diradical:





5





Each  $R^4$  independently is selected from:

5                    H;  
                  F;  
                   $CH_3$ ;  
                   $CF_3$ ;  
                   $C(O)H$ ;  
                   $CN$ ;  
10                     $HO$ ;  
                   $CH_3O$ ;  
                   $C(F)H_2O$ ;  
                   $C(H)F_2O$ ; and  
                   $CF_3O$ ;

15                     $t$  is an integer of 0 or 1;  
                   $V^1$  is selected from:

                  a 5-membered heteroarylenyl;  
                   $CH_2C\equiv C$ ;  
                   $CF_2C\ C\equiv C$ ;

20                     $C(O)O$ ;  
                   $C(S)O$ ;  
                   $C(O)N(R^5)$ ; and  
                   $C(S)N(R^5)$ ;

Q, when bonded to a nitrogen atom in group D, is selected from:

25                     $OC(O)$ ;  
                   $CH(R^6)C(O)$ ;  
                   $OC(NR^6)$ ;

$\text{CH}(\text{R}^6)\text{C}(\text{NR}^6)$ ;

$\text{N}(\text{R}^6)\text{C}(\text{O})$ ;

$\text{N}(\text{R}^6)\text{C}(\text{S})$ ;

$\text{N}(\text{R}^6)\text{C}(\text{NR}^6)$ ;

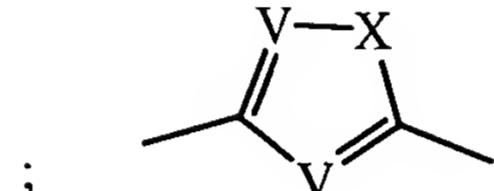
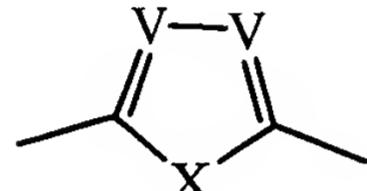
5  $\text{SC}(\text{O})$ ;

$\text{CH}(\text{R}^6)\text{C}(\text{S})$ ;

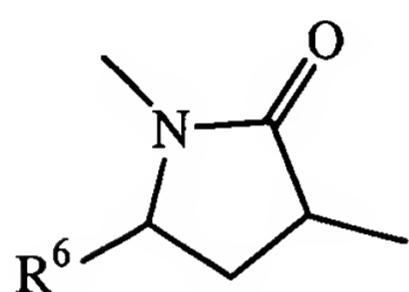
$\text{SC}(\text{NR}^6)$ ;

$\text{C}\equiv\text{CCH}_2$ ;

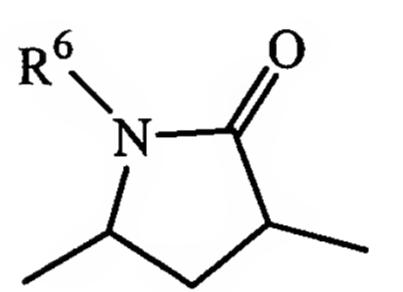
$\text{C}\equiv\text{CCF}_2$ ;



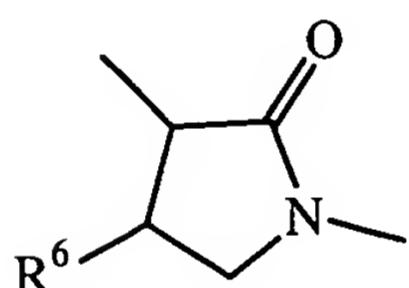
;



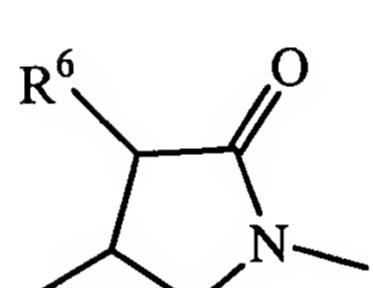
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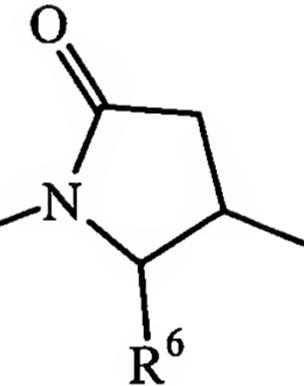
;



;



;



;

Q, when bonded to a carbon atom in group D, is as defined above and may further be selected from:

$\text{OCH}_2$ ;

15  $\text{N}(\text{R}^6)\text{CH}_2$ ;

trans-(H)C=C(H);

cis-(H)C=C(H);

$\text{C}\equiv\text{C}$ ;

$\text{CH}_2\text{C}\equiv\text{C}$ ; and

20  $\text{CF}_2\text{C}\equiv\text{C}$ ;

Each X independently is O, S, N(H), or N(C<sub>1</sub>-C<sub>6</sub> alkyl);

Each V independently is C(H) or N;

Each R<sup>5</sup> independently is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

$R^6$  is H,  $C_1$ - $C_6$  alkyl,  $C_3$ - $C_6$  cycloalkyl; 3- to 6-membered heterocycloalkyl;

phenyl; benzyl; or 5- or 6-membered heteroaryl;

Each “substituted” group contains from 1 to 4 substituents, each independently on a carbon or nitrogen atom, independently selected from:

5             $C_1$ - $C_6$  alkyl;  
           $C_2$ - $C_6$  alkenyl;  
           $C_2$ - $C_6$  alkynyl;  
           $C_3$ - $C_6$  cycloalkyl;  
           $C_3$ - $C_6$  cycloalkylmethyl;

10            Phenyl;  
          Phenylmethyl;  
          3- to 6-membered heterocycloalkyl;  
          3- to 6-membered heterocycloalkylmethyl;  
          cyano;

15             $CF_3$ ;  
           $(C_1$ - $C_6$  alkyl)- $OC(O)$ ;  
           $HOCH_2$ ;  
           $(C_1$ - $C_6$  alkyl)- $OCH_2$ ;  
           $H_2NCH_2$ ;

20             $(C_1$ - $C_6$  alkyl)- $N(H)CH_2$ ;  
           $(C_1$ - $C_6$  alkyl) $_2$ - $NCH_2$ ;  
           $N(H)_2C(O)$ ;  
           $(C_1$ - $C_6$  alkyl)- $N(H)C(O)$ ;  
           $(C_1$ - $C_6$  alkyl) $_2$ - $NC(O)$ ;

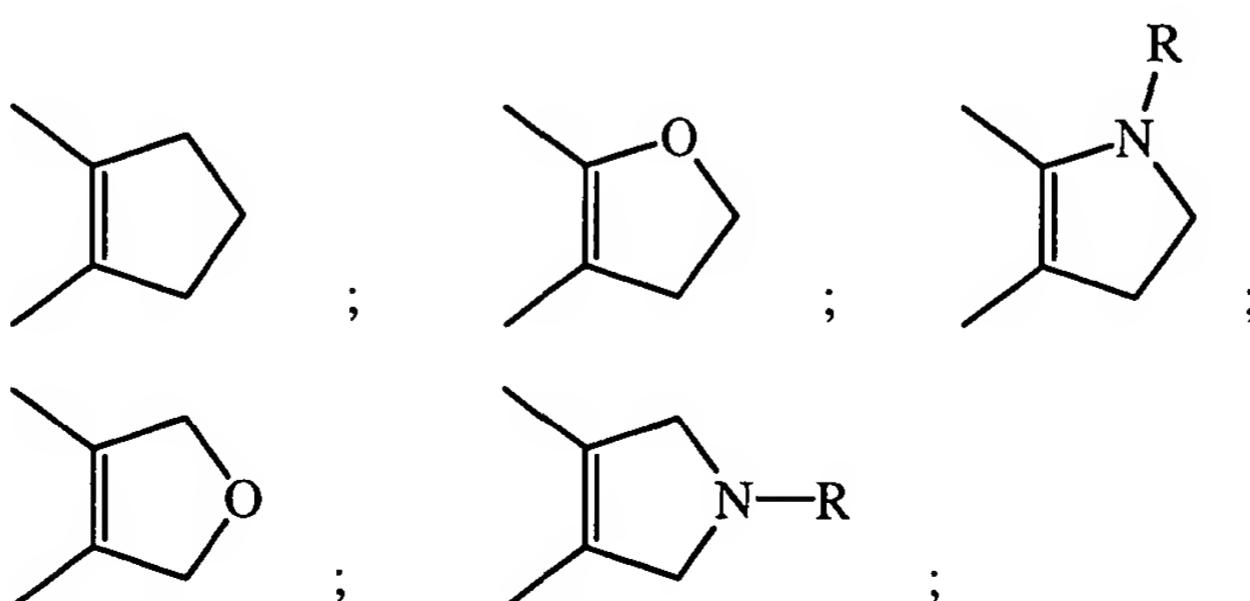
25             $N(H)_2C(O)N(H)$ ;  
           $(C_1$ - $C_6$  alkyl)- $N(H)C(O)N(H)$ ;  
           $N(H)_2C(O)N(C_1$ - $C_6$  alkyl);  
           $(C_1$ - $C_6$  alkyl)- $N(H)C(O)N(C_1$ - $C_6$  alkyl);  
           $(C_1$ - $C_6$  alkyl) $_2$ - $NC(O)N(H)$ ;

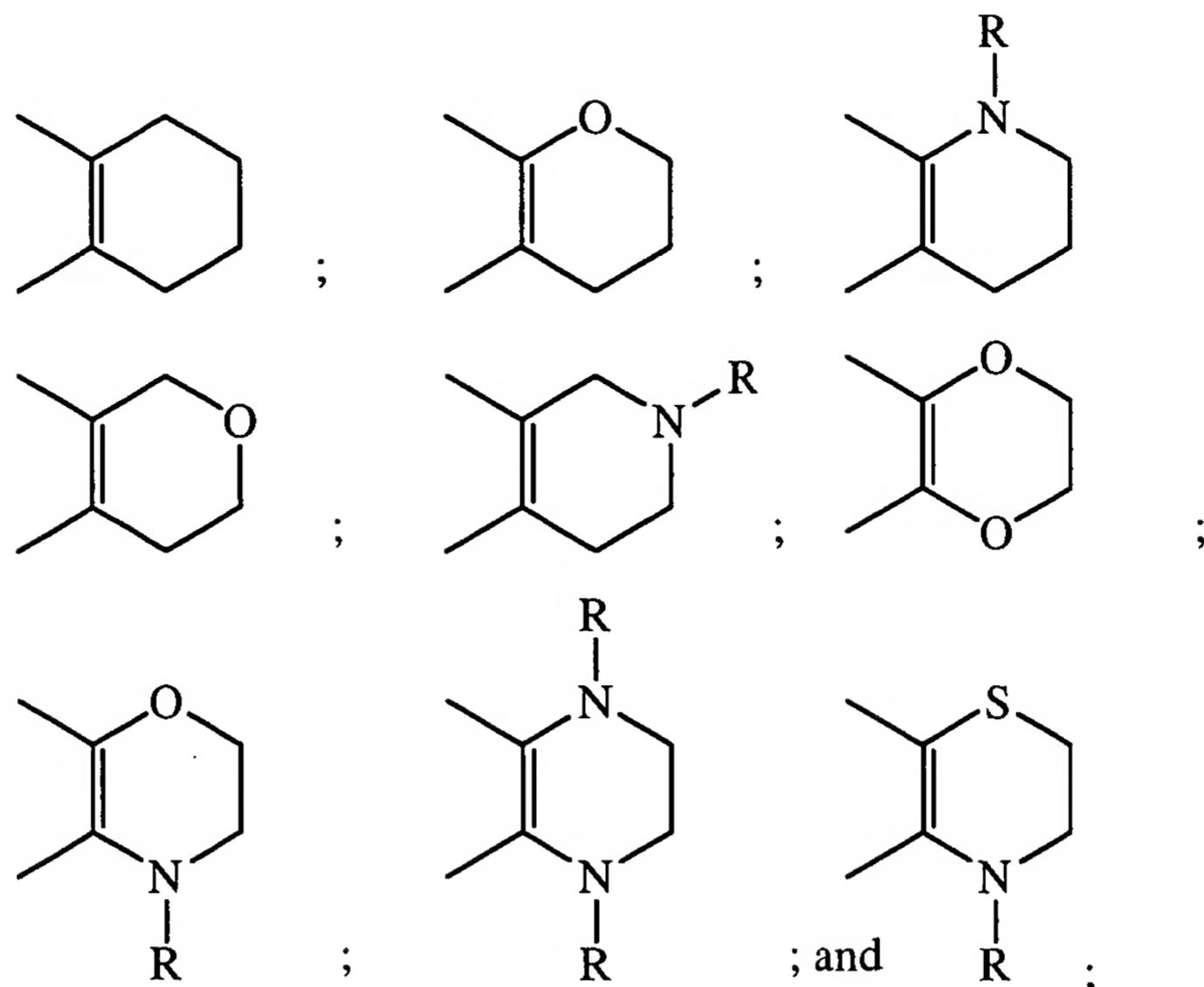
30             $(C_1$ - $C_6$  alkyl) $_2$ - $NC(O)N(C_1$ - $C_6$  alkyl);  
           $N(H)_2C(O)O$ ;  
           $(C_1$ - $C_6$  alkyl)- $N(H)C(O)O$ ;

(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>-NC(O)O;  
HO;  
(C<sub>1</sub>-C<sub>6</sub> alkyl)-O;  
CF<sub>3</sub>O;  
5 CF<sub>2</sub>(H)O;  
CF(H)<sub>2</sub>O;  
H<sub>2</sub>N;  
(C<sub>1</sub>-C<sub>6</sub> alkyl)-N(H);  
(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>-N;  
10 O<sub>2</sub>N;  
(C<sub>1</sub>-C<sub>6</sub> alkyl)-S;  
(C<sub>1</sub>-C<sub>6</sub> alkyl)-S(O);  
(C<sub>1</sub>-C<sub>6</sub> alkyl)-S(O)<sub>2</sub>;  
(C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>-NS(O)<sub>2</sub>;  
15 (C<sub>1</sub>-C<sub>6</sub> alkyl)-S(O)<sub>2</sub>-N(H)-C(O)-(C<sub>1</sub>-C<sub>8</sub> alkylene)<sub>m</sub>; and  
(C<sub>1</sub>-C<sub>6</sub> alkyl)-C(O)-N(H)-S(O)<sub>2</sub>-(C<sub>1</sub>-C<sub>8</sub> alkylene)<sub>m</sub>;

wherein each substituent on a carbon atom may further be independently selected from:

20 Halo;  
HO<sub>2</sub>C; and  
OCH<sub>2</sub>O, wherein each O is bonded to adjacent carbon atoms to form a 5-membered ring;  
wherein 2 substituents may be taken together with a carbon atom to which they are both bonded to form the group C=O;  
25 wherein two adjacent, substantially sp<sup>2</sup> carbon atoms may be taken together with a diradical substituent to form a cyclic diradical selected from:





Each m independently is an integer of 0 or 1;

5 R is H or C<sub>1</sub>-C<sub>6</sub> alkyl;

wherein each 5-membered heteroarylenyl independently is a 5-membered ring

containing carbon atoms and from 1 to 4 heteroatoms selected from 1 O, 1 S, 1 NH, 1 N(C<sub>1</sub>-C<sub>6</sub> alkyl), and 4 N, wherein the O and S atoms are not both present, and wherein the heteroarylenyl may optionally be

10 unsubstituted or substituted with 1 substituent selected from fluoro, methyl, hydroxy, trifluoromethyl, cyano, and acetyl;

wherein each heterocycloalkyl is a ring that contains carbon atoms and 1 or 2

heteroatoms independently selected from 2 O, 1 S, 1 S(O), 1 S(O)<sub>2</sub>, 1 N, 2 N(H), and 2 N(C<sub>1</sub>-C<sub>6</sub> alkyl), and wherein when two O atoms or one O

15 atom and one S atom are present, the two O atoms or one O atom and one S atom are not bonded to each other, and wherein the ring is saturated or optionally contains one carbon-carbon or carbon-nitrogen double bond;

wherein each 5-membered heteroaryl contains carbon atoms and from 1 to 4

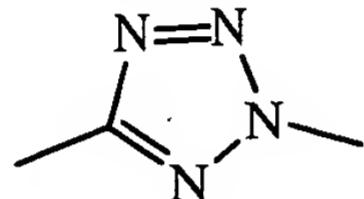
heteroatoms independently selected from 1 O, 1 S, 1 N(H), 1 N(C<sub>1</sub>-C<sub>6</sub>

20 alkyl), and 4 N, and each 6-membered heteroaryl contains carbon atoms and 1 or 2 heteroatoms independently selected from N, N(H), and N(C<sub>1</sub>-C<sub>6</sub> alkyl), and 5- and 6-membered heteroaryl are monocyclic rings; and 9- and 10-membered heteroaryl are 6,5-fused and 6,6-fused bicyclic rings,

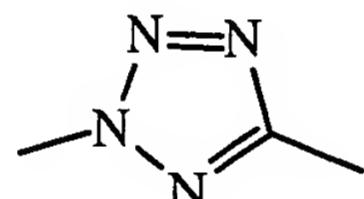
respectively, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other;

5 wherein with any (C<sub>1</sub>-C<sub>6</sub> alkyl)<sub>2</sub>-N group, the C<sub>1</sub>-C<sub>6</sub> alkyl groups may be optionally taken together with the nitrogen atom to which they are attached to form a 5- or 6-membered heterocycloalkyl; and wherein each group and each substituent recited above is independently selected.

10 2. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein V<sup>1</sup> is



15 3. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein V<sup>1</sup> is



20 4. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is N(R<sup>6</sup>)C(O).

5. The compound according to Claim 1, or a pharmaceutically acceptable salt thereof, wherein Q is C≡C.

25 6. The compound according to any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein at least one of R<sup>1</sup> and R<sup>2</sup> is independently selected from:

Phenyl-(C<sub>1</sub>-C<sub>6</sub> alkyl); and

Substituted phenyl-(C<sub>1</sub>-C<sub>6</sub> alkyl);

wherein each group and each substituent is independently selected.

7. The compound according to according to any one of Claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein at least one of R<sup>1</sup> and R<sup>2</sup> is independently selected from:

5 5-, 6-, 9-, and 10-membered heteroaryl-(C<sub>1</sub>-C<sub>6</sub> alkylene); and

Substituted 5-, 6-, 9-, and 10-membered heteroaryl-(C<sub>1</sub>-C<sub>6</sub> alkylene);

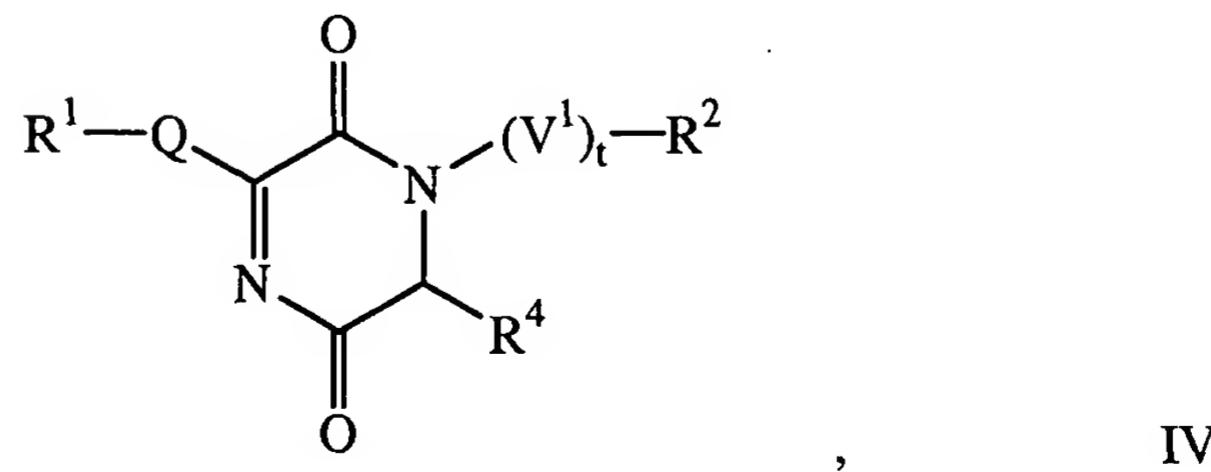
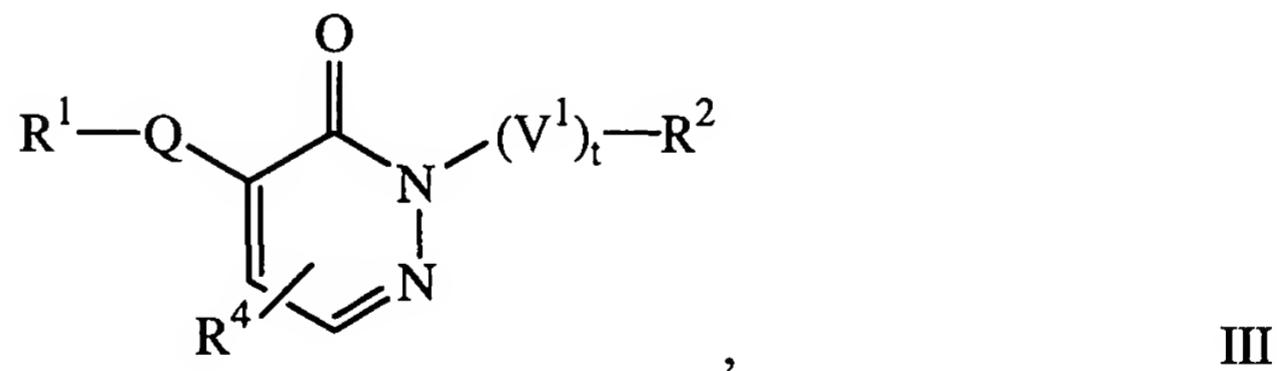
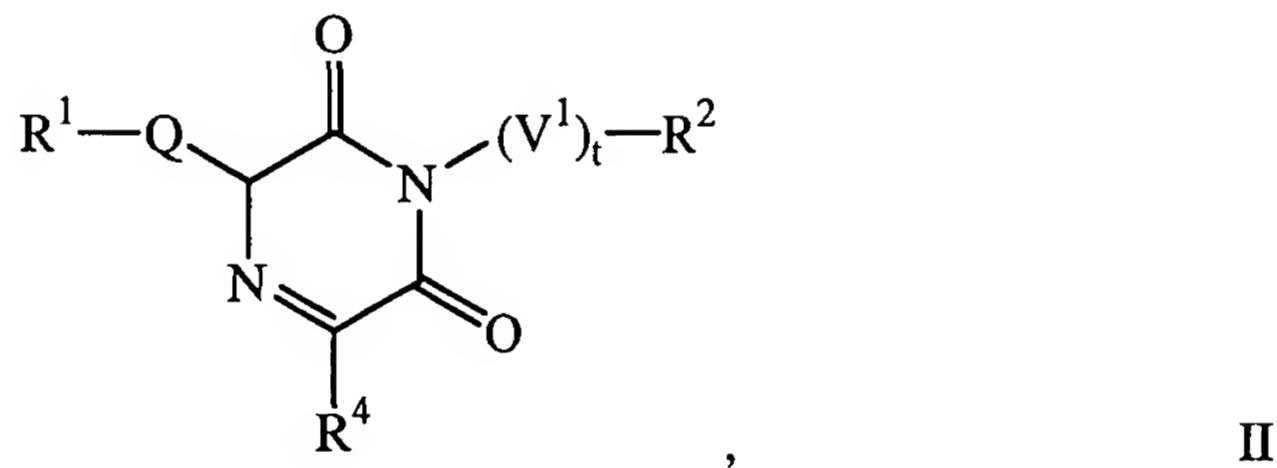
wherein each heteroaryl contains carbon atoms and from 1 to 4 heteroatoms

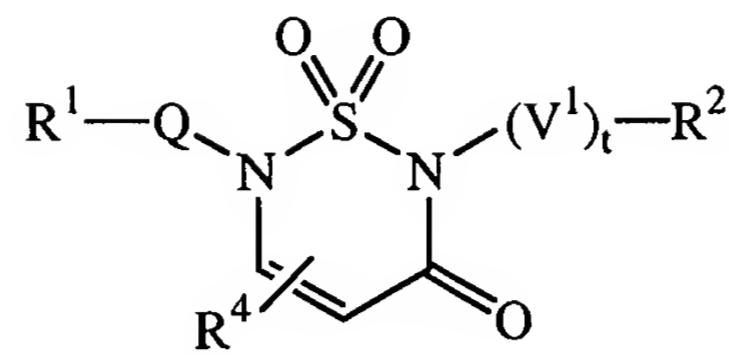
independently selected from 1 O, 1 S, 1 N(H), 1 N(C<sub>1</sub>-C<sub>6</sub> alkyl), and 4 N, and 5- and 6-membered heteroaryl are monocyclic rings and 9- and 10-membered heteroaryl are 6,5-fused and 6,6-fused bicyclic rings,

10 respectively, wherein at least 1 of the 2 fused rings of a bicyclic ring is aromatic, and wherein when the O and S atoms both are present, the O and S atoms are not bonded to each other; and

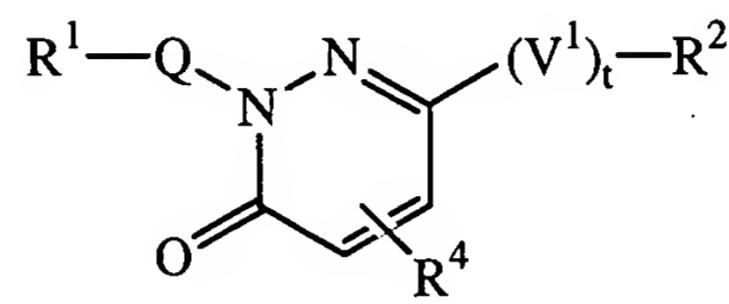
wherein each group and each substituent is independently selected.

15 8. A compound of Formula II, III, IV, V, or VI





, V



, VI

or a pharmaceutically acceptable salt thereof.

5        9. The compound of Formula II according to Claim 8, selected from:

4-[5-(3-Benzylcarbamoyl-2,6-dioxo-3,6-dihydro-2H-pyrazin-1-yl)-tetrazol-2-yl]-benzoic acid;

4-(5-{2,6-Dioxo-3-[(pyridin-4-ylmethyl)-carbamoyl]-3,6-dihydro-2H-pyrazin-1-yl}-tetrazol-2-yl)-benzoic acid;

10      4-[3-(3-Benzylcarbamoyl-2,6-dioxo-3,6-dihydro-2H-pyrazin-1-yl)-prop-2-ynyl]-benzoic acid;

4-(3-{2,6-Dioxo-3-[(pyridin-4-ylmethyl)-carbamoyl]-3,6-dihydro-2H-pyrazin-1-yl}-prop-2-ynyl)-benzoic acid;

4-{2-[2,6-Dioxo-3-(3-phenyl-prop-1-ynyl)-3,6-dihydro-2H-pyrazin-1-yl]-oxazol-5-yl}-benzoic acid;

15      4-{2-[3-(3-Imidazol-1-yl-prop-1-ynyl)-2,6-dioxo-3,6-dihydro-2H-pyrazin-1-yl]-oxazol-4-yl}-benzoic acid;

4-{3-[2,6-Dioxo-3-(3-phenyl-prop-1-ynyl)-3,6-dihydro-2H-pyrazin-1-yl]-prop-2-ynyl}-benzoic acid;

20      4-{3-[3-(3-Imidazol-1-yl-prop-1-ynyl)-2,6-dioxo-3,6-dihydro-2H-pyrazin-1-yl]-prop-2-ynyl}-benzoic acid;

4-({[2,6-Dioxo-3-(5-phenyl-oxazol-2-yl)-3,6-dihydro-2H-pyrazine-1-carbonyl]-amino}-methyl)-benzoic acid;

4-{3-[2,6-Dioxo-3-(5-phenyl-oxazol-2-yl)-3,6-dihydro-2H-pyrazin-1-yl]-prop-2-ynyl}-benzoic acid;

25      4-{5-[2,6-Dioxo-3-(4-phenyl-oxazol-2-yl)-3,6-dihydro-2H-pyrazin-1-yl]-tetrazol-2-yl}-benzoic acid; and

4-{3-[2,6-Dioxo-3-(4-phenyl-oxazol-2-yl)-3,6-dihydro-2H-pyrazin-1-yl]-prop-2-ynyl}-benzoic acid;  
or a pharmaceutically acceptable salt thereof.

5 10. The compound of Formula III according to Claim 8, selected from:  
4-[5-(5-Benzylcarbamoyl-6-oxo-6H-pyridazin-1-yl)-tetrazol-2-yl]-benzoic acid;  
4-(5-{6-Oxo-5-[(pyridin-4-ylmethyl)-carbamoyl]-6H-pyridazin-1-yl}-tetrazol-2-yl)-benzoic acid;  
10 4-[3-(5-Benzylcarbamoyl-6-oxo-6H-pyridazin-1-yl)-prop-2-ynyl]-benzoic acid;  
4-(3-{6-Oxo-5-[(pyridin-4-ylmethyl)-carbamoyl]-6H-pyridazin-1-yl}-prop-2-ynyl)-benzoic acid;  
15 4-{2-[6-Oxo-5-(3-phenyl-prop-1-ynyl)-6H-pyridazin-1-yl]-oxazol-5-yl}-benzoic acid;  
4-{2-[5-(3-Imidazol-1-yl-prop-1-ynyl)-6-oxo-6H-pyridazin-1-yl]-oxazol-4-yl}-benzoic acid;  
4-{3-[6-Oxo-5-(3-phenyl-prop-1-ynyl)-6H-pyridazin-1-yl]-prop-2-ynyl}-benzoic acid;  
20 4-{3-[5-(3-Imidazol-1-yl-prop-1-ynyl)-6-oxo-6H-pyridazin-1-yl]-prop-2-ynyl}-benzoic acid;  
4-({[6-Oxo-5-(5-phenyl-oxazol-2-yl)-6H-pyridazine-1-carbonyl]-amino}-methyl)-benzoic acid;  
25 4-{3-[6-Oxo-5-(5-phenyl-oxazol-2-yl)-6H-pyridazin-1-yl]-prop-2-ynyl}-benzoic acid;  
4-{5-[6-Oxo-5-(4-phenyl-oxazol-2-yl)-6H-pyridazin-1-yl]-tetrazol-2-yl}-benzoic acid; and  
4-{3-[6-Oxo-5-(4-phenyl-oxazol-2-yl)-6H-pyridazin-1-yl]-prop-2-ynyl}-benzoic acid;  
30 or a pharmaceutically acceptable salt thereof.

11. A pharmaceutical composition, comprising a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.
- 5 12. The pharmaceutical composition according to Claim 11, comprising a compound according to Claim 9 or 10, or a pharmaceutically acceptable salt thereof, admixed with a pharmaceutically acceptable carrier, excipient, or diluent.
- 10 13. A method for treating osteoarthritis or rheumatoid arthritis, comprising administering to a patient suffering from osteoarthritis or rheumatoid arthritis a nontoxic effective amount of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof.
- 15 14. The method according to Claim 13, wherein the compound administered is a compound according to Claim 9 or 10, or a pharmaceutically acceptable salt thereof.